22
Hydrogen-Mediated Carbon–Carbon Bond Formation Catalyzed by Rhodium

Chang-Woo Cho and Michael J. Krische

22.1
Introduction and Mechanistic Considerations

The development of direct catalytic methods for reductive carbon–carbon bond formation has emerged as the subject of intensive investigation [1–10]. The catalytic hydrometallative reductive coupling of alkenes [1], alkynes [2, 3], allenes [4], conjugated enones [5–7], conjugated dienes [8–10] and conjugated enynes [11] to carbonyl partners and imines has been achieved using silanes, stannanes, boranes and alanes as terminal reductant. The use of such terminal reductants mandates stoichiometric byproduct generation. Related hydrogen-mediated transformations would proceed with complete levels of atom economy [12]. However, while metal catalysts capable of reversible transfer hydrogenation have been applied to the development of C–C bond formations predicated on dehydrogenation-trapping-rehydrogenation [13], true hydrogen-mediated reductive C–C bond formations only have been achieved for processes involving migratory insertion of carbon monoxide, for example, alkene hydroformylation and the Fischer-Tropsch reaction [14, 15].

The question persists as to whether the organometallic intermediates that appear transiently during the course of catalytic hydrogenation can be intercepted and re-routed to products of C–C bond formation. In the case of rhodium-catalyzed alkene hydroformylation, a key feature appears to be the involvement of mono-hydride-based catalytic cycles, wherein the formation of (alkyl)(hydrido)metal intermediates occurs *subsequent* to C–C bond formation. In contrast, conventional dihydride-based hydrogenation cycles generally afford (alkyl)(hydrido)metal intermediates in *advance* of potential C–C bond formation. For such dihydride-based hydrogenation cycles, the capture of hydrogenation intermediates is likely untenable due to rapid C–H reductive elimination. This may account, in part, for the exceptional rarity of hydrogen-mediated C–C bond formation in the absence of carbon monoxide [15].

Recent studies from our laboratory demonstrate the feasibility of hydrogen-mediated C–C bond formation under "CO-free conditions." Here, at least two

The Handbook of Homogeneous Hydrogenation.
Edited by J. G. de Vries and C. J. Elsevier

ISBN: 978-3-527-31161-3

distinct mechanistic pathways potentially operate. Initial studies on hydrogen-mediated reductive aldol coupling demonstrate that conventional hydrogenation pathways are suppressed through the use of cationic rhodium precatalysts in the presence of a mild base. Such conditions are believed to promote heterolytic hydrogen activation (H_2+M–X → M–H+HX) [16, 20]. Monohydride-mediated hydrometallation should furnish organometallic species that do not possess hydride ligands, disabling direct C–H reductive elimination manifolds and extending the lifetimes of the organometallic intermediates obtained upon hydrometallation to facilitate their capture. Hence, one strategy for hydrogen-mediated C–C bond formation involves the hydrogenation of reactants using catalysts that operate *via* monohydride-based catalytic cycles. A second strategy for hydrogen-mediated C–C bond formations takes advantage of the fact that hydrogen activation can be quite slow for certain conventional hydrogenation catalysts. Here, oxidative coupling of the reacting partners prior to hydrogenation activation becomes feasible [17] (Scheme 22.1).

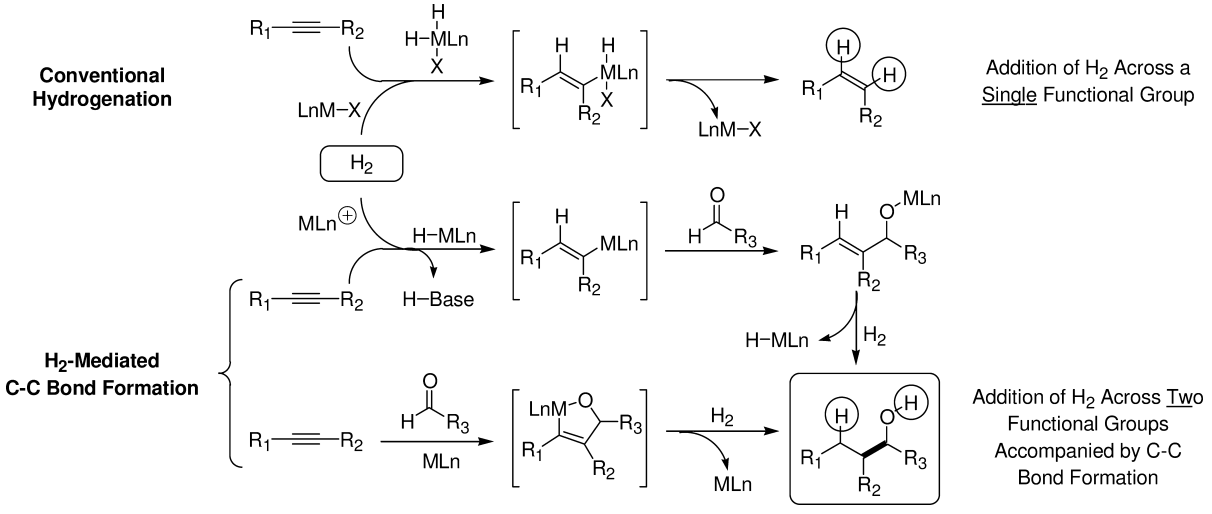
Among homogeneous hydrogenation catalysts, those based on rhodium are especially well studied [18–20, 28]. Whereas neutral rhodium(I)-complexes such as Wilkinson's catalyst induce *homolytic* hydrogen activation [18, 19], the use of cationic rhodium(I) complexes in conjunction with basic additives is believed to promote *heterolytic* activation pathways [20]. Heterolytic hydrogen activation by cationic rhodium complexes presumably is owed to the enhanced acidity of the cationic dihydrides that result upon oxidative addition in comparison to their neutral counterparts [21]. Thus, heterolytic hydrogen activation is believed to occur through a two-stage process involving hydrogen oxidative addition followed by base-induced H–X reductive elimination [22] (Scheme 22.2).

Hydrogen activation is rate-determining for enantioselective hydrogenations employing cationic rhodium catalysts [28]. This observation is significant given that closely related cationic rhodium(I) complexes are known to catalyze a variety of C–C bond formations believed to proceed through the initial oxidative coupling of π-unsaturated partners to furnish metallocyclic intermediates [17]. Accordingly, tandem oxidative coupling-metallocycle hydrogenolysis strategies toward hydrogen-mediated C–C bond formation have proven fruitful (*vide supra*).

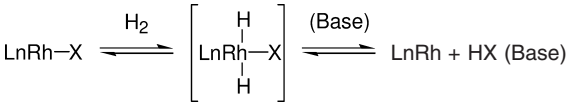
Here, a comprehensive overview of hydrogen-mediated C–C bond formation under CO-free conditions is presented [23]. This emergent family of reductive couplings now encompasses:

- the intra- and intermolecular reductive coupling of enone and enal pronucleophiles with aldehyde and ketone partners [24];
- the intermolecular reductive coupling of 1,3-cyclohexadiene with α-ketoaldehydes [25];
- the intermolecular reductive coupling of 1,3-enynes and 1,3-diynes with α-ketoaldehydes and iminoacetates [26]; and
- the reductive cyclization of 1,6-diynes and 1,6-enynes [27].

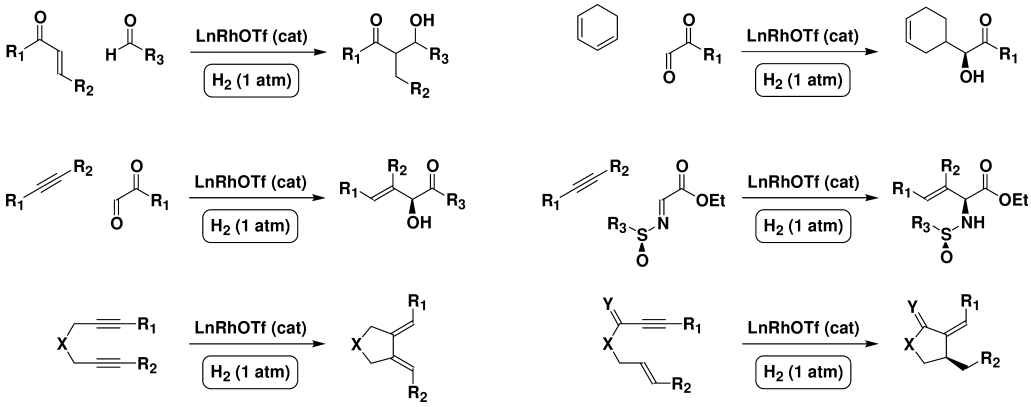
These results establish catalytic hydrogenation as a powerful and mechanistically novel means of catalytic C–C bond formation, and support the feasibility



Scheme 22.1 Potential mechanistic pathways for hydrogen-mediated C–C bond formation.



Scheme 22.2 Formal heterolytic hydrogen activation *via* deprotonation of a dihydride intermediate.



Scheme 22.3 Hydrogen-mediated C–C bond formations catalyzed by rhodium.

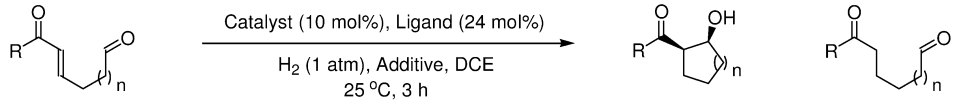
of developing a broad new class of catalytic reductive C–C bond formations (Scheme 22.3).

22.2
Reductive Coupling of Conjugated Enones and Aldehydes

22.2.1
Intramolecular Reductive Aldolization

Initial studies pertaining to the Rh-catalyzed aldol cycloreduction under hydrogenation conditions are consistent with the bifurcated catalytic mechanism depicted in Schemes 22.1 and 22.4 [24a]. Catalytic hydrogenation of the indicated enone-aldehyde using the neutral complex $Rh(PPh_3)_3Cl$ provides only trace quantities of the aldol product due to competitive 1,4-reduction via conventional hydrogenation. In contrast, rhodium salts that embody increased cationic character, such as $Rh^I(COD)_2OTf$, provide almost equal proportions of aldol and 1,4-reduction products. Finally, when $Rh^I(COD)_2OTf$ is used in conjunction with substoichiometric quantities of the mildly basic additive potassium acetate, the proportion of aldol product is increased such that simple 1,4-reduction manifolds are nearly fully suppressed. The observed *syn*-diastereoselectivity suggests intermediacy of a *Z*-enolate and a Zimmerman-Traxler-type transition state. These optimized conditions

Table 22.1 Partitioning of aldolization and 1,4-reduction pathways depends critically on the use of cationic Rh-complexes and mildly basic additives. [a)]

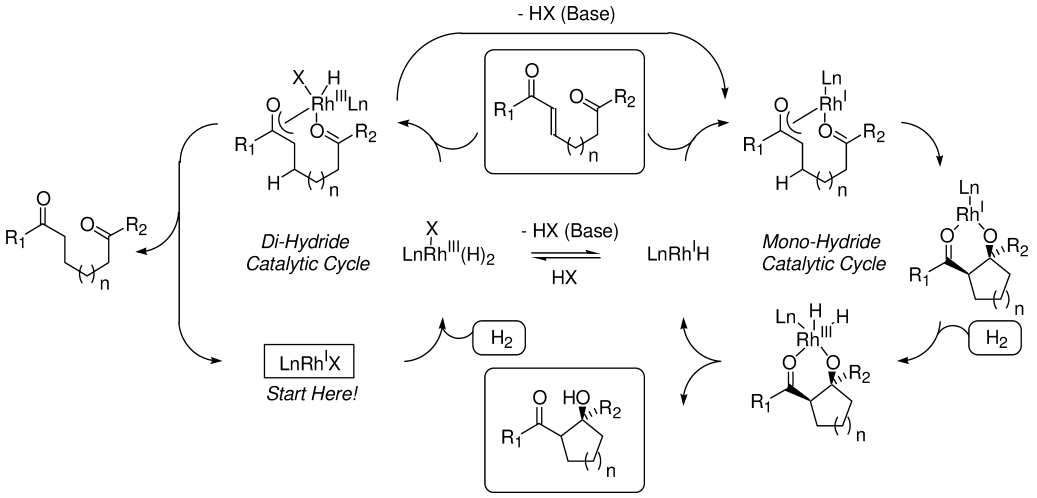


Substrate	Catalyst	Ligand	Additive (mol%)	Yield Aldol (Syn-Anti)	Yield 1,4-Reduction
n=2, R=Ph	$Rh(PPh_3)Cl$	–	–	1% (99:1)	95%
n=2, R=Ph	$Rh(COD)_2OTf$	PPh_3	–	21% (99:1)	25%
n=2, R=Ph	$Rh(COD)_2OTf$	PPh_3	KOAc (30%)	59% (58:1)	21%
n=2, R=Ph	$Rh(COD)_2OTf$	$(p\text{-}CF_3Ph)_3P$	–	57% (14:1)	22%
n=2, R=Ph	**$Rh(COD)_2OTf$**	**$(p\text{-}CF_3Ph)_3P$**	**KOAc (30%)**	**89% (10:1)**	**0.1%**
n=2, R=*p*-MeOPh	$Rh(COD)_2OTf$	$(p\text{-}CF_3Ph)_3P$	KOAc (30%)	74% (5:1)	3%
n=2, R=2-Naphthyl	$Rh(COD)_2OTf$	$(p\text{-}CF_3Ph)_3P$	KOAc (30%)	90% (10:1)	1%
n=2, R=2-thiophenyl	$Rh(COD)_2OTf$	$(p\text{-}CF_3Ph)_3P$	KOAc (30%)	76% (19:1)	2%
n=2, R=2-Furyl	$Rh(COD)_2OTf$	$(p\text{-}CF_3Ph)_3P$	KOAc (30%)	70% (6:1)	10%
n=1, R=Ph	$Rh(COD)_2OTf$	$(p\text{-}CF_3Ph)_3P$	KOAc (30%)	71% (24:1)	1%
n=2, R=CH_3	$Rh(COD)_2OTf$	$(p\text{-}CF_3Ph)_3P$	KOAc (30%)	65% (1:5)	–

a) As product ratios were found to vary with surface to volume ratio of the reaction mixture, all transformations were conducted on 1.48 mmol scale in 50 mL round bottomed flasks.

proved general for the cycloreduction of aromatic, heteroaromatic and aliphatic enone substrates to form five- and six-membered ring products (Table 22.1).

The pronounced effect of basic additives on partitioning of the aldolization and 1,4-reduction manifolds suggests that enolate-hydrogen reductive elimination pathways are disabled through deprotonation of the (hydrido)metal intermediates $LnRh^{III}X(H)_2$ or $(enolato)Rh^{III}X(H)Ln$. Thus, as proposed by Osborn and Schrock [20], deprotonation shifts the catalytic mechanism from a dihydride-based cycle to a monohydride-based cycle. In the former case, 1,4-reduction products would predominate. In the latter case, owing to the absence of (alkyl)(hydrido)rhodium intermediates, capture of the rhodium enolate through its addition to the appendant aldehyde is facilitated. The following control experiments were performed. Exposure of the simple 1,4-reduction product to the reaction conditions does not result in aldolization. Conversely, re-exposure of the aldol product to the reaction conditions does not result in retroaldolization. Finally, exposure of the substrate to standard reaction conditions in the *absence* of hydrogen does not afford products of Morita-Baylis-Hillman cyclization. For the sake of clarity, the catalytic mechanism indicated in Scheme 22.4 has been simplified. For example, equilibria involving association of the substrate to the catalyst prior to hydrogen activation are omitted, although such equilibria are known to be an important feature of the enantioselective hydrogenation of dehydroamino acids employing cationic rhodium catalysts [28] (Scheme 22.4).



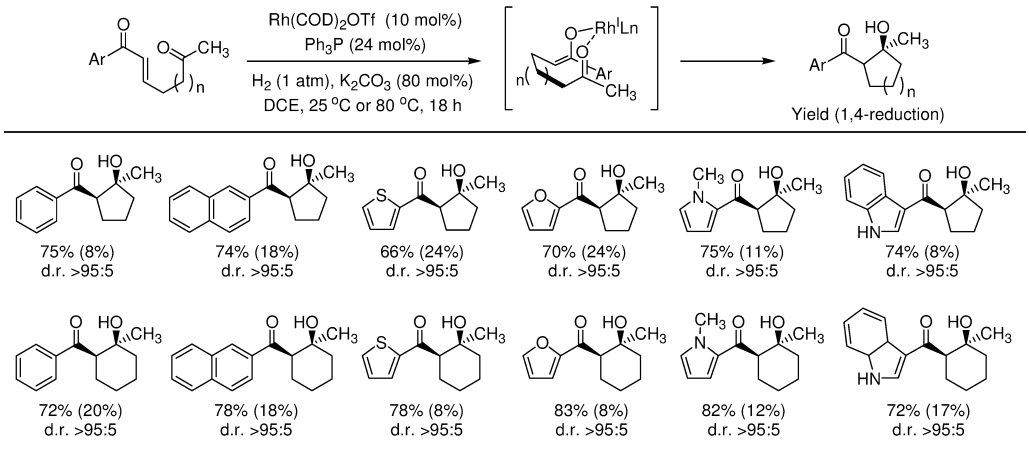
Scheme 22.4 A bifurcated mechanism accounting for the effect of basic additives.

In order to explore the scope of this hydrogen-mediated aldol addition methodology, additions to ketone acceptors were explored. Because ketones are less electrophilic than aldehydes, competitive conventional hydrogenation was anticipated to be problematic. Indeed, upon exposure of keto-enones to basic hydrogenation conditions, the formation of five- and six-membered ring aldol products is accompanied by substantial quantities of conventional hydrogenation products. As retro-aldolization does not occur upon resubmission of the aldol products to the reaction conditions, enone hydrogenation must occur prior to carbonyl addition. Nevertheless, serviceable yields of the ketone aldol products are obtained. Moreover, very high levels of *syn*-diastereoselectivity are observed, which again are attributed to the intermediacy of a *Z*-enolate and a Zimmerman-Traxler-type transition state. While aldolization proceeds readily at ambient temperature, more reproducible ratios of aldol and 1,4-reduction product are observed at 80 °C [24 b] (Table 22.2).

In order to gain further insight into the reaction mechanism, the indicated oxygen-tethered keto-enone was subjected to basic hydrogenation conditions under 1 atmos. elemental deuterium. Deuterium incorporation is observed at the former enone *β*-position exclusively. In addition to mono-deuterated material (81% composition), doubly-deuterated (8% composition) and non-deuterated materials (11% composition) are observed. These data suggest reversible hydrometallation in the case of keto-enone substrates. Consistent with the mechanism depicted in Scheme 22.4, deuterium is not incorporated at the *α*-position of the aldol product [24 b] (Scheme 22.5).

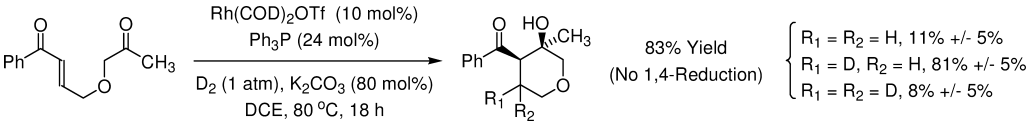
For the cycloreduction of keto-enones, competitive 1,4-reduction in response to the reduced electrophilicity of the carbonyl partner is observed. Diones are more susceptible to addition by viture of inductive effects and the relief of di-

Table 22.2 Catalytic hydrogen-mediated reductive aldol cyclization of keto-enones.

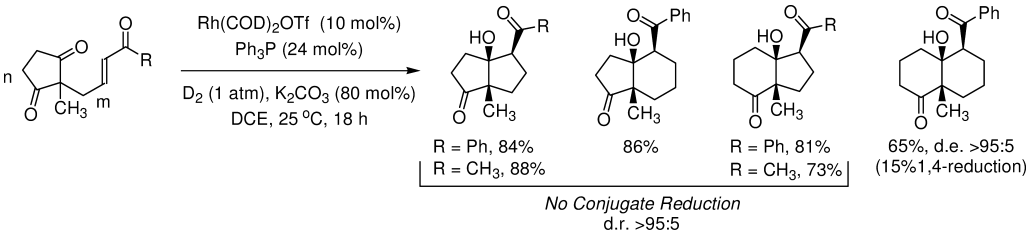


a) As product ratios were found to vary with surface-to-volume ratio of the reaction mixture, all transformations were conducted on 1.48 mmol scale in 13×100-mm sealed test tubes.

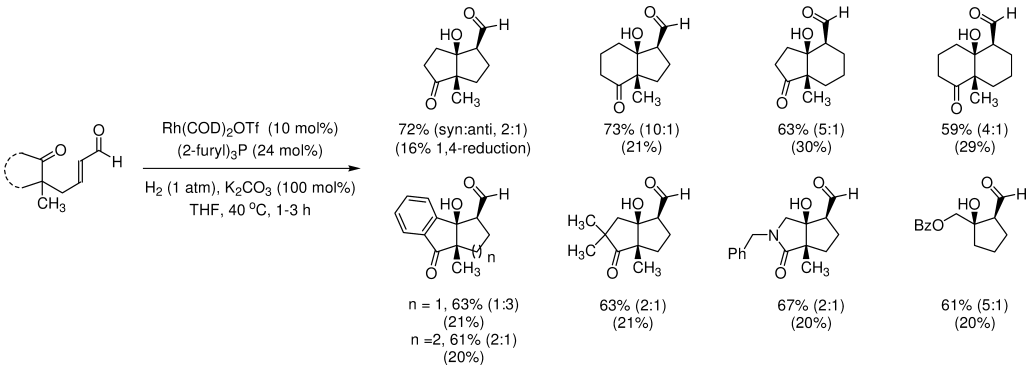
pole-dipole interactions. Accordingly, catalytic hydrogenation of dione-containing substrates affords the corresponding aldol products in good yield and with excellent *syn*-diastereoselectivity for both benzoyl- and acetyl-containing enones. Simple 1,4-reduction only accompanies formation of the strained *cis*-decalone ring system [24b] (Scheme 22.6).



Scheme 22.5 Deuterium-labeling studies suggest reversible hydrometallation for keto-enone substrates.



Scheme 22.6 Catalytic hydrogen-mediated reductive aldol cyclization of enone-diones.



Scheme 22.7 Catalytic addition of metallo-aldehyde enolates to ketones.

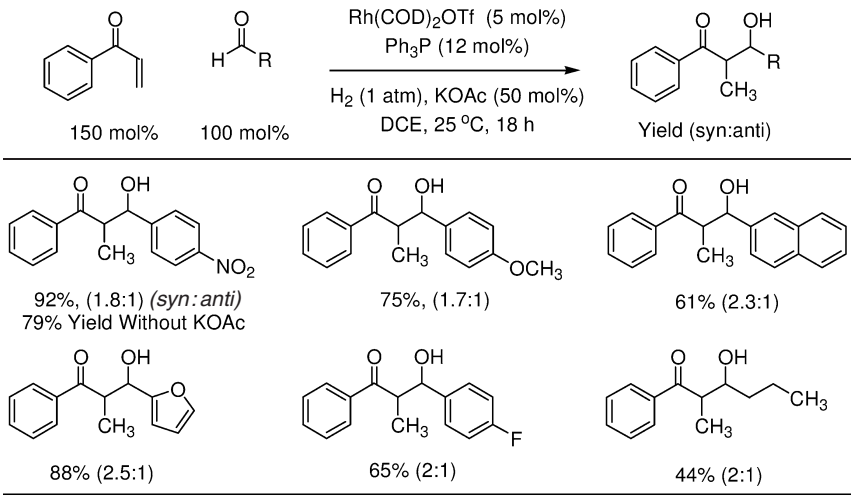
Perhaps the most elusive variant of the aldol reaction involves the addition of metallo-aldehyde enolates to ketones. A single stoichiometric variant of this transformation is known [29]. As aldolization is driven by chelation, intramolecular addition to afford a robust transition metal aldolate should bias the enolate-aldolate equilibria toward the latter [30, 31]. Indeed, upon exposure to basic hydrogenation conditions, keto-enal substrates provide the corresponding cycloaldol products, though competitive 1,4-reduction is observed (Scheme 22.7) [24 d].

22.2.2
Intermolecular Reductive Aldolization

In principle, the presumed rhodium(I) enolates that occur transiently during the course of enone hydrogenation may: (i) engage in aldolization; or (ii) hydrogenolytically cleave *via* oxidative addition of hydrogen followed by reductive elimination. In principle, intermolecular capture of such hydrogenation intermediates should suffer due to increasingly competitive conventional hydrogenation. In practice, only a modest excess of vinyl ketone is required to offset conventional hydrogenation manifolds. For example, hydrogenation of phenyl vinyl ketone (PVK) (150 mol%) in the presence of aromatic and heteroaromatic aldehydes (100 mol%) provides good yields of the corresponding aldol products. As PVK is prone toward anionic polymerization, these results are especially noteworthy. Consistent with the bifurcated mechanism depicted in Scheme 22.4, the addition of potassium acetate significantly increases the yield of aldol product (Table 22.3) [24 a].

In the case of methyl vinyl ketone (MVK), similar reactivity is observed. Exposure of MVK (150 mol%) and *p*-nitrobenzaldehyde to basic hydrogenation conditions provides the corresponding aldol product in good yield, though poor diastereoselectivity is observed [24 a]. Remarkably, upon use of *tris*(2-furyl)phosphine as ligand and Li_2CO_3 as basic additive, the same aldol product is formed with high levels of *syn*-selectivity [24 e]. Addition of MVK to activated ketones such as 1-(3-bromophenyl)propane-1,2-dione is accomplished under similar con-

Table 22.3 Use of phenyl vinyl ketone (PVK) in intermolecular hydrogen-mediated reductive aldol coupling.



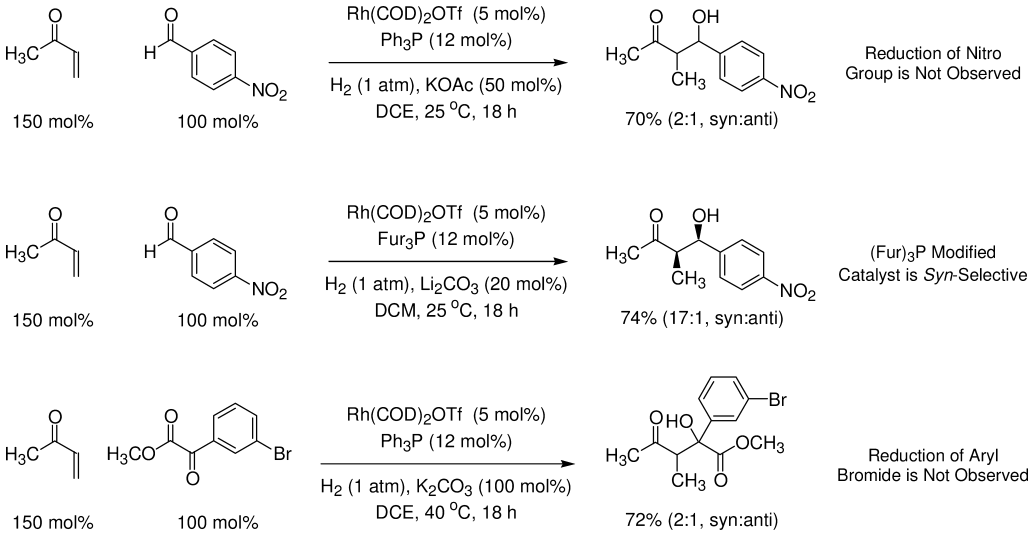
a) As product ratios were found to vary with surface-to-volume ratio of the reaction mixture, all transformations were conducted on 1.0 mmol scale in 50-mL round-bottomed flasks.

ditions [24e]. Notably, neither reduction of the nitro group or aryl bromide is observed (Scheme 22.8).]

Intermolecular cross aldolization of metallo-aldehyde enolates typically suffers from polyaldolization, product dehydration and competitive Tishchenko-type processes [32]. While such cross-aldolizations have been achieved through amine catalysis and the use of aldehyde-derived enol silanes [33], the use of aldehyde enolates in this capacity is otherwise undeveloped. Under hydrogenation conditions, acrolein and crotonaldehyde serve as metallo-aldehyde enolate precursors, participating in selective cross-aldolization with α-ketoaldehydes [24c]. The resulting β-hydroxy-γ-ketoaldehydes are highly unstable, but may be trapped *in situ* through the addition of methanolic hydrazine to afford 3,5-disubstituted pyridazines (Table 22.4).

To corroborate the proposed mechanism, the catalytic reductive aldol coupling of acrolein with phenyl glyoxal monohydrate was performed under 1 atmos. elemental deuterium. Exposure of the aldol product to excess hydrazine *in situ* results in formation of the pyridazine, which incorporates precisely one deuterium atom in a manner consistent with the general mechanism proposed in Scheme 22.4 (Scheme 22.9).

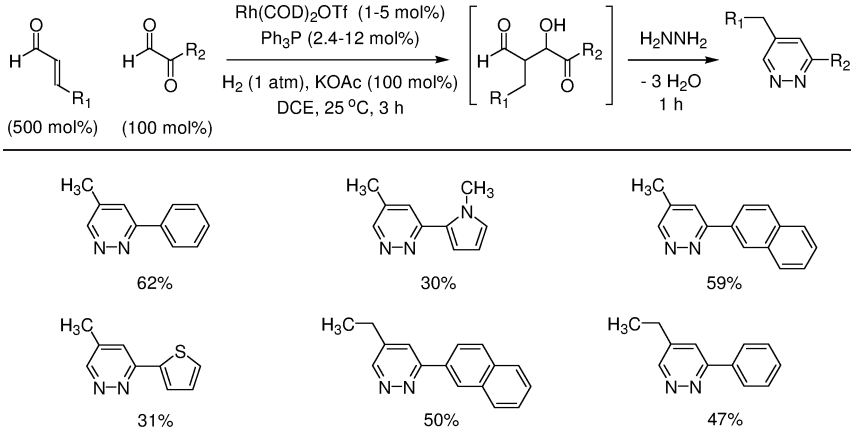
Thus far, the use of acrylates and related acyl derivatives as nucleophilic partners in hydrogen-mediated reductive aldol coupling has been unsuccessful due to competitive conventional hydrogenation. Although the mechanistic basis of these results remains unclear, it may be speculated that for acrylates and struc-



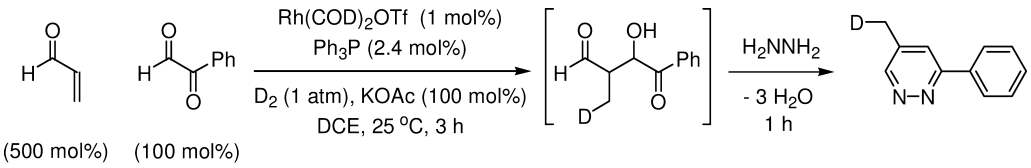
a) As product ratios were found to vary with surface-to-volume ratio of the reaction mixture, all transformations were conducted on 1.0 mmol scale in 50-mL round-bottomed flasks.

Scheme 22.8 Use of methyl vinyl ketone (MVK) in intermolecular hydrogen-mediated reductive aldol coupling.[a)]

Table 22.4 Use of acrolein and crotonaldehyde in intermolecular hydrogen-mediated reductive aldol coupling.

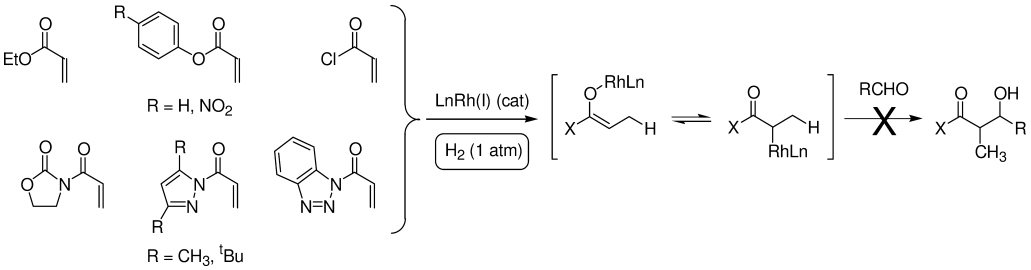


a) As product ratios were found to vary with surface-to-volume ratio of the reaction mixture, all transformations were conducted on 1.0 mmol scale in 50-mL round-bottomed flasks.



a) As product ratios were found to vary with surface-to-volume ratio of the reaction mixture, all transformations were conducted on 1.0 mmol scale in 50-mL round-bottomed flasks.

Scheme 22.9 Intermolecular reductive aldol coupling of acrolein and phenyl glyoxal under a D_2 atmosphere.[a)]



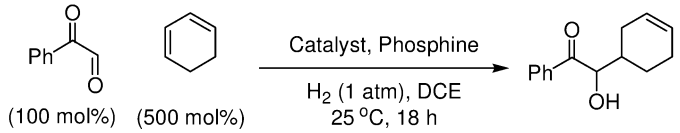
Scheme 22.10 Attempted reductive aldol coupling of ethyl acrylate and related acyl derivatives.

tural relatives possessing heteroatom substitution at the acyl position, the haptomeric equilibrium pertaining to the *O*-bound and *C*-bound forms of the rhodium(I) enolate is biased toward the latter. As aldol addition should occur by way of the *O*-bound enolate in accordance with the Zimmerman-Traxler model, the intervention of a *C*-bound enolate may diminish the rate of aldolization to the point that competitive conventional hydrogenation predominates.

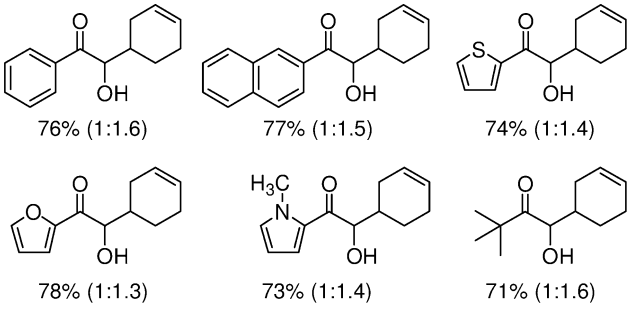
22.3
Reductive Coupling of 1,3-Cyclohexadiene and α-Ketoaldehydes

Given the structural homology of conjugated enones and 1,3-dienes, the reductive coupling of 1,3-cyclohexadiene and phenyl glyoxal was examined under hydrogenation conditions [22]. Optimization studies again reveal the requirement of cationic rhodium catalysts. Whereas hydrogenation of 1,3-cyclohexadiene and phenyl glyoxal using Wilkinson's catalyst provides products of simple reduction, a 61% yield of reductive coupling product is obtained using $Rh(COD)_2OTf$ with PPh_3 as ligand. When $(p\text{-}CH_3OPh)_3P$ is employed as ligand, the yield of coupling product increases to 77%. Related cationic complexes, such as $Rh(COD)_2BF_4$, exhibit similar efficiencies when used in conjunction with $(p\text{-}CH_3OPh)_3P$. Under optimized conditions, the catalytic reductive coupling of 1,3-cyclohexadiene with di-

Table 22.5 Catalytic reductive coupling of 1,3-cyclohexadiene with alkyl, aryl and heteroaryl α-ketoaldehydes.

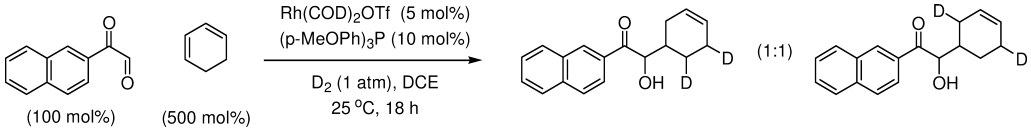


Entry	Catalyst (mol%)	Ligand (mol%)	Yiedl (%)
1	$Rh(PPh_3)_3Cl$ (10%)	–	–
2	$Rh(COD)_2OTf$ (10%)	Ph_3P (20%)	61
3	$Rh(COD)_2OTf$ (10%)	$(p\text{-}CF_3Ph)_3P$ (20%)	24
4	$Rh(COD)_2OTf$ (10%)	$(p\text{-}CH_3OPh)_3P$ (20%)	77
5	$Rh(COD)_2BF_4$ (10%)	$(p\text{-}CH_3OPh)_3P$ (20%)	79
6	**$Rh(COD)_2OTf_4$ (5%)**	**$(p\text{-}CH_3OPh)_3P$ (10%)**	**76**

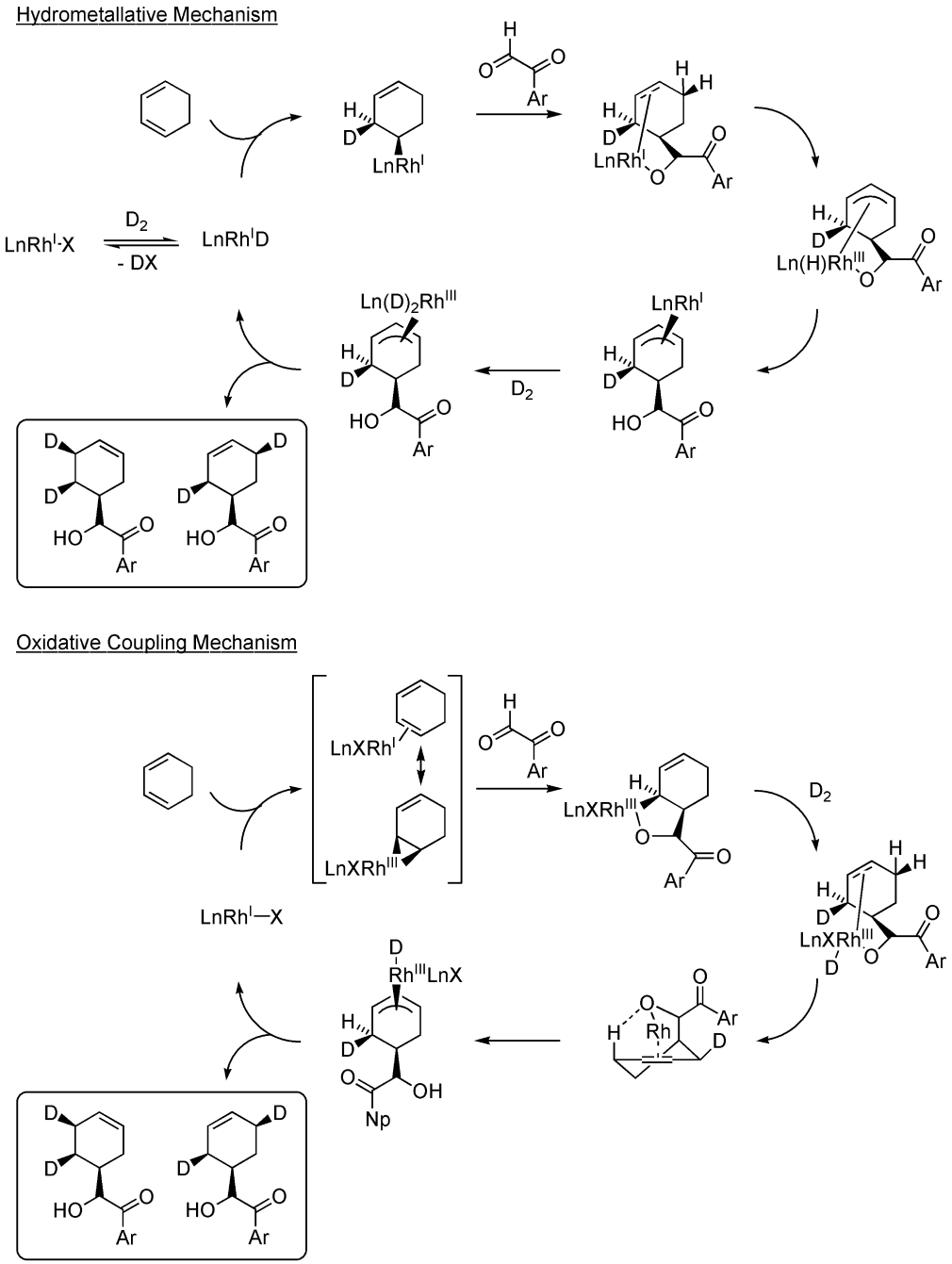


verse α-ketoaldehydes was examined. Aryl, heteroaryl and aliphatic α-ketoaldehydes provide reductive coupling products in good yield. Notably, basic additives are not required, suggesting that heterolytic hydrogen activation may not be operative (Table 22.5).

Deuterium-labeling studies reveal that the reductive coupling of 1,3-cyclohexadiene with α-ketoaldehydes occurs through a mechanism very different than that postulated for related enone-aldehyde couplings. Reductive coupling of 1,3-cyclohexadiene with 2-naphthyl glyoxal under an atmosphere of D_2(g) results in the incorporation of precisely two deuterium atoms as an equimolar distribution of 1,2- and 1,4-regioisomers. The relative stereochemistry of the deuterated materials could not be assigned (Scheme 22.11).



Scheme 22.11 Reductive coupling of 1,3-cyclohexadiene and 2-naphthyl glyoxal under an atmosphere of D_2(g).



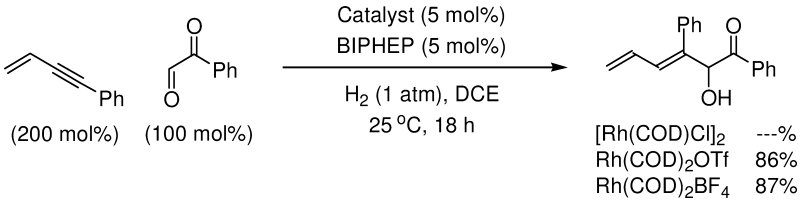
Scheme 22.12 Possible mechanisms for the reductive coupling of 1,3-cyclohexadiene and 2-naphthyl glyoxal under an atmosphere of D_2(g).

The mechanism initially proposed involves diene hydrometallation from a monohydride derived via heterolytic hydrogen activation (Scheme 22.12, upper). Here, diene deuterometallation gives rise to a homo-allyl rhodium intermediate, which engages in carbonyl addition to afford a rhodium alkoxide. The indicated regiochemistry of C–C bond formation is consistent with that observed by Loh in the nickel-catalyzed reductive coupling of 1,3-cyclohexadiene with aldehydes [9e]. Additionally, as observed by Mori, the presence of 1,3-cyclohexadiene induces 1,4-regiochemistry in nickel-promoted diene-aldehyde cyclizations [8b]. Allylic C–H insertion provides a rhodium(III) π-allyl, which upon O–H reductive elimination gives rise to a rhodium(I) π-allyl. Similar allylic C–H insertions are observed in metal-catalyzed alkene isomerization [34]. Finally, oxidative addition of elemental deuterium followed by C–D reductive elimination completes the catalytic cycle. The intermediacy of rhodium a π-allyl is required to account for the incorporation of precisely two deuterium atoms as an equimolar distribution of 1,2- and 1,4-regioisomers (Scheme 22.12, upper).

A related mechanistic proposal involves diene-glyoxal oxidative coupling (Scheme 22.12, lower). Here, complexation by low-valent rhodium(I) confers nucleophilic character to the bound diene *via* backbonding, as suggested by the Dewar-Chatt-Duncanson model for alkene coordination [35]. For low-valent *early* transition metals, such "back-bonding" is driven by the stability associated with a d^0-electronic configuration. For example, as demonstrated by the Kulinkovich reaction, complexation of olefins by Ti(II) causes them to behave as vicinal dianions: Ti(II)(olefin) $\leftrightarrow$ Ti(IV)(metallocyclopropane) [36]. For *late* transition metals, the driving force associated with attaining a noble gas electronic configuration is absent, perhaps accounting for the requirement of highly activated electrophilic partners such as α-ketoaldehydes. In any case, addition of the diene to the glyoxal provides the formal product of oxidative coupling. This oxarhodacycle may react with deuterium via sigma bond metathesis to afford a rhodium alkoxide, which abstracts an allylic hydrogen to provide a rhodium π-allyl complex. Subsequent C–D reductive elimination delivers the dideuterated products as an equimolar distribution of regioisomers (Scheme 22.12, lower). Recently, this diene-glyoxal coupling was performed under an atmosphere of HD(g) as the terminal reductant. The coupling product was found to incorporate a single molecule of deuterium, distributed over the same three carbons found when D_2(g) was used as reductant. These data disqualify the initially disclosed hydrometallative mechanism, and strongly support the latter mechanism involving direct oxidative coupling.

22.4
Reductive Coupling of Conjugated Enynes and Diynes with Activated Aldehydes and Imines

The reductive coupling of 1,3-cyclohexadiene and α-ketoaldehydes, which occurs without over-reduction of the olefinic product, suggests the feasibility of utilizing more highly unsaturated pronucleophiles in the form of 1,3-enynes. In the

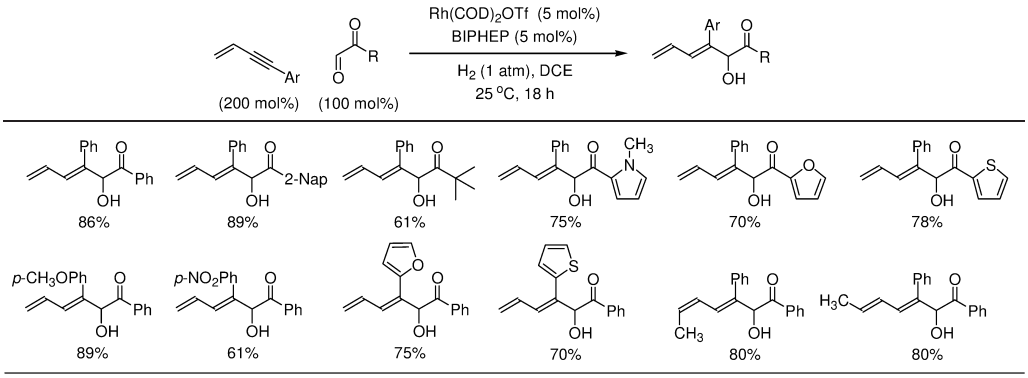


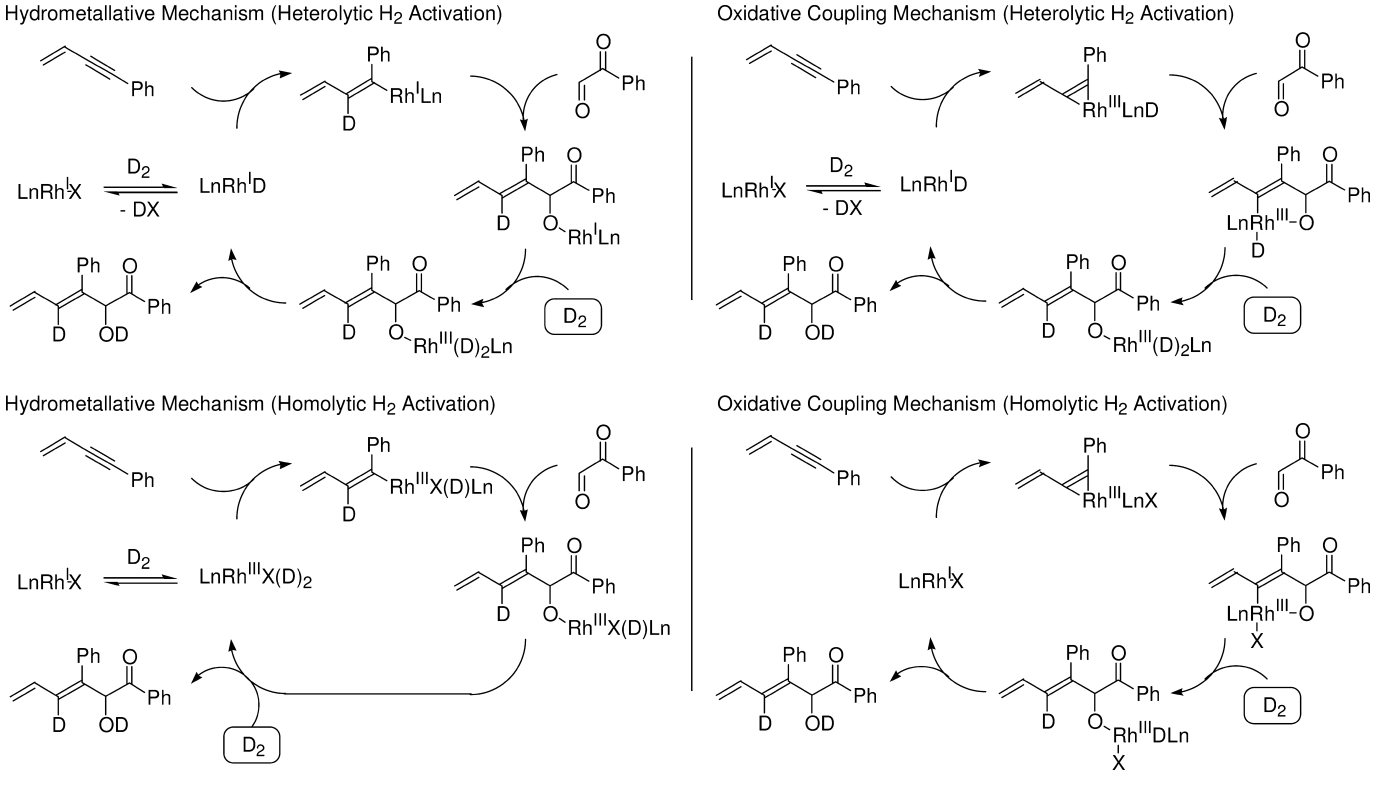
Scheme 22.13 Reductive coupling of 1-phenyl but-3-en-1-yne with phenyl glyoxal.

event, the reaction conditions optimized for the cyclohexadiene-α-ketoaldehyde couplings, which employ (p-MeOPh)$_3$P as ligand, proved ineffective at promoting the coupling of 1-phenylbut-3-en-1-yne and phenyl glyoxal. However, under otherwise identical conditions, the use of bidentate ligands such as BIPHEP provides the products of reductive coupling in excellent yield. Under optimized conditions, the coupling proceeds smoothly to afford diene-containing products as single regio- and stereoisomers. Over-reduction of the diene-containing products is not observed. Presumably, upon complete consumption of glyoxal, excess enyne nonproductively coordinates rhodium, dramatically retarding the rate of any further reduction. As for the diene couplings, basic additives are not required. Additionally, reductive coupling fails upon use of neutral Rh(I) precatalysts, such as [Rh(COD)Cl]$_2$ (Scheme 22.13, Table 22.6).

Catalytic reductive coupling of 1-phenyl but-3-en-1-yne with phenyl glyoxal conducted under 1 atmos. elemental deuterium provides the *mono*-deuterated product in 85% yield. It is instructive to compare hydrometallative and oxidative coupling mechanisms involving both heterolytic and homolytic deuterium activation. For the hydrometallative mechanism involving heterolytic deuterium activation, direct alkyne deuterometallation to afford the vinyl rhodium intermediate is followed by carbonyl addition and hydrogenolytic cleavage of the resulting

Table 22.6 Reductive coupling of assorted 1,3-enynes with alkyl, aryl and heteroaryl α-ketoaldehydes.

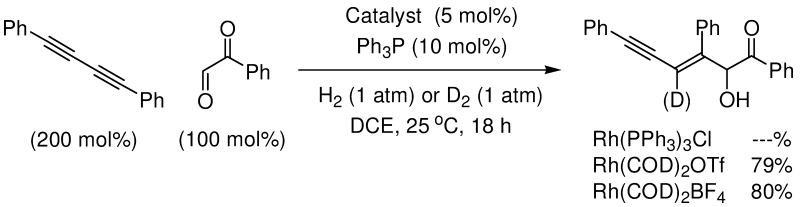




Scheme 22.14 Plausible mechanisms for the reductive coupling of 1-phenyl but-3-en-1-yne with phenyl glyoxal under an atmosphere of D_2(g).

Rh(I)-alkoxide. Notably, this mechanism requires deuterometallation to occur with complete regioselection (Scheme 22.14, top-left). The corresponding hydrometallative mechanism involving homolytic deuterium activation also requires completely regioselective deuterometallation. Moreover, carbonyl addition must compete favorably with C–D reductive elimination (Scheme 22.14, bottom-left). A mechanism involving heterolytic hydrogen activation followed by oxidative coupling of the reactants is plausible. Here, C–D reductive elimination of the resulting (hydrido)Rh(III)-oxametallocyclopentene followed by hydrogenolytic cleavage of rhodium alkoxide completes the catalytic cycle (Scheme 22.14, top-right). Finally, direct oxidative coupling of the reactants with subsequent hydrogenolytic cleavage of the resulting metallocycle may be envisaged. This latter mechanism requires deuterium activation by a rhodium(III) intermediate. An increasing body of evidence supports participation of organorhodium(III) complexes in σ-bond metathesis pathways [37], including reactions with hydrogen [37c]. In the case of the hydrometallative mechanisms, C–H bond formation precedes C–C bond formation. In the case of the oxidative coupling mechanisms, the converse is true. The oxidative coupling mechanism better accounts for the regiochemistry of reductive coupling and is preferred on the basis of related mechanistic studies (*vide supra*). In principle, it should be possible to discriminate between heterolytic and homolytic hydrogen activation modes *via* H_2–D_2 and HD isotope crossover experiments. However, rapid exchange of the hydroxylic protons and deuterons under the reaction conditions renders this prospect untenable (Scheme 22.14).

1,3-Diynes also participate in highly regio- and stereoselective reductive couplings to aryl, heteroaryl and aliphatic glyoxals under catalytic hydrogenation conditions [26b]. Unlike the corresponding reaction of 1,3-enynes, both *mono*- and *bis*(phosphines) may serve as ligands. Consistent with the requirement of cationic rhodium(I) catalysts, $Rh(COD)_2OTf$ and $Rh(COD)_2BF_4$ are viable catalysts, while $Rh(PPh_3)_3Cl$ is not. Remarkably, formation of the highly unsaturated 1,3-enyne products is not accompanied by over-reduction. As previously stated, it would appear that upon complete consumption of glyoxal, excess enyne nonproductively coordinates rhodium, retarding the rate of further reduction. Reductive coupling performed under an atmosphere of D_2 provides the indicated mono-deuterated product. This result may be interpreted on the basis of the mechanisms outlined in Scheme 22.14 (Scheme 22.15).

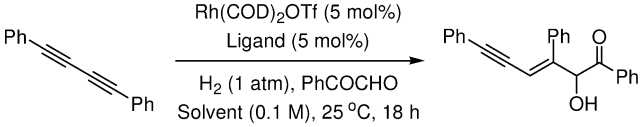


Scheme 22.15 Reductive coupling of diphenylbutadiyne with phenyl glyoxal.

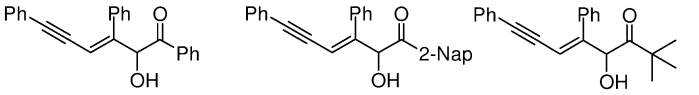
A highly enantioselective variant of this transformation has been developed using the commercially available chiral *bis*(phosphine) (*R*)-Cl-MeO-BIPHEP. Optimization studies pertaining to the enantioselective transformation reveal that high levels of asymmetric induction are critically dependent upon the dihedral angle of the diphenylphosphino moieties of the ligand. Under optimized conditions, coupling products are produced in 71–77% yield and 86–95% enantiomeric excess. Notably, highly enantioselective C–C bond formation is achieved at ambient temperature and pressure (Table 22.7).

Under optimum conditions identified for enantioselective coupling, non-symmetric 1,3-diynes react with marked levels of regioselectivity. Specifically, for 1-phenyl-4-alkyl 1,3-diynes, coupling occurs preferentially at the aromatic terminus (Table 22.8). Competition experiments provide some insight into the mechanistic basis for such regioselectivity. Catalytic hydrogenation of phenyl glyoxal in the presence of equimolar quantities of 1,4-diphenylbutadiene and 1,4-diphenylbut-3-en-1-yne results in coupling to the more highly unsaturated enyne partner. Similarly, catalytic hydrogenation of phenyl glyoxal in the presence of equimolar quantities of 1,4-diphenylbut-3-en-1-yne and 1,4-diphenylbutadiyne

Table 22.7 Enantioselective catalytic reductive coupling of 1,3-diynes with alkyl, aryl and heteroaryl α-ketoaldehydes.



Entry	Ligand	Solvent	Yield (%)	e.e. (%)
1	(*R*)-BINAP	DCE	72	47
2	(*R*)-Phanephos	DCE	79	67
3	(*R*)-Cl-OMe-BIPHEP	DCE	74	76
4	(*R*)-Cl-OMe-BIPHEP	EtOH	69	80
5	(*R*)-Cl-OMe-BIPHEP	THF	67	82
6	**(*R*)-Cl-OMe-BIPHEP**	**PhH**	**74**	**91**



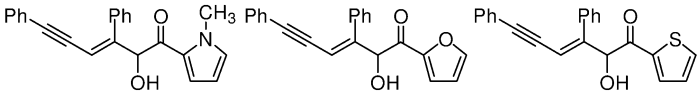
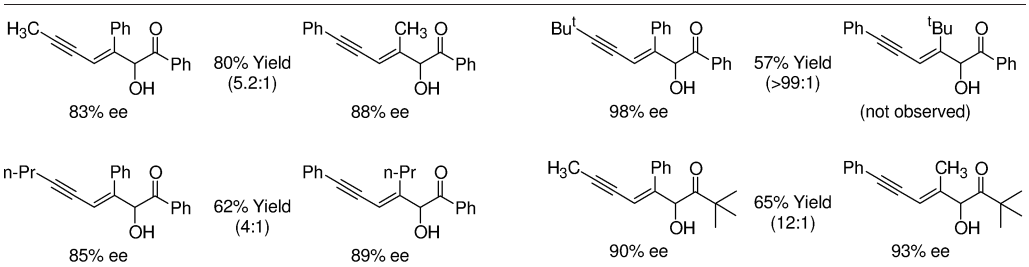
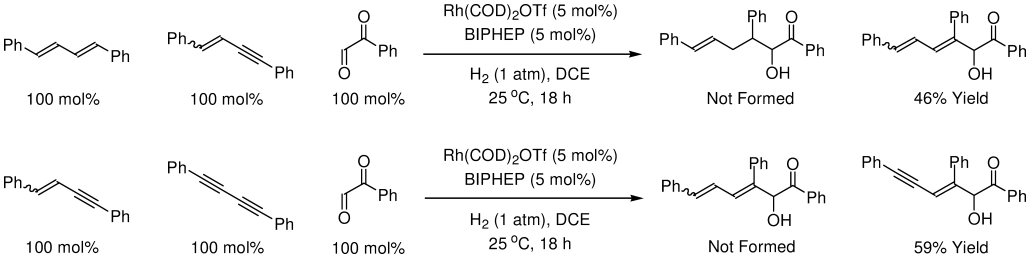


Table 22.8 Regioselective reductive coupling of non-symmetric 1,3-diynes to various α-ketoaldehydes.



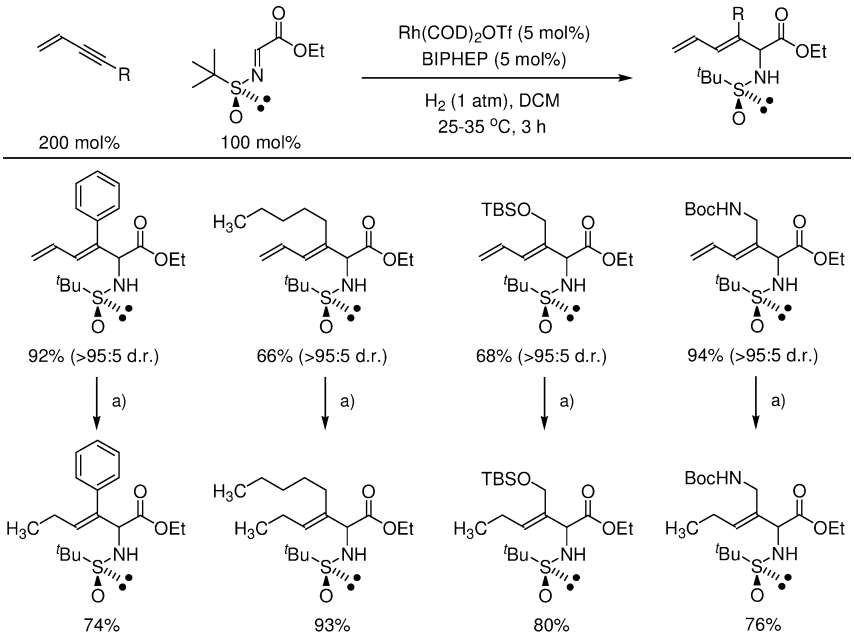
results in coupling to the more highly unsaturated diyne partner. Chemoselective coupling to the more highly unsaturated pronucleophile suggests preferential coordination of low-valent rhodium to the most π-acidic reactant. Moreover, for non-symmetric 1,3-diynes, regioselective C–C bond formation occurs at the terminus of the diyne that embodies the lowest LUMO energy. Hence, the chemo- and regioselectivity of reductive coupling may be explained by the Dewar-Chatt-Duncanson model for alkyne coordination [35] – that is, coordination of low-valent rhodium is driven by backbonding, with nucleophilic character developing at positions where backbonding occurs most effectively (Scheme 22.16).

Rhodium-catalyzed hydrogenation of 1,3-enynes and 1,3-diynes in the presence of ethyl (*N-tert*-butanesulfinyl)iminoacetate and ethyl (*N*-2,4,6-triisopropylbenzenesulfinyl)iminoacetate, respectively, results in reductive coupling to afford unsaturated α-amino acid esters in good to excellent yields with exceptional levels of stereocontrol [26c] (Tables 22.9 and 22.10). Remarkably, the reductive coupling of non-symmetric 1,3-diynes to iminoacetates occurs with complete levels of regioselectivity. Further hydrogenation of the diene side chain using Wilkinson's catalyst provides the corresponding β,γ-unsaturated amino acid esters. Exhaustive hydrogenation of both the diene- and enyne-containing side chains



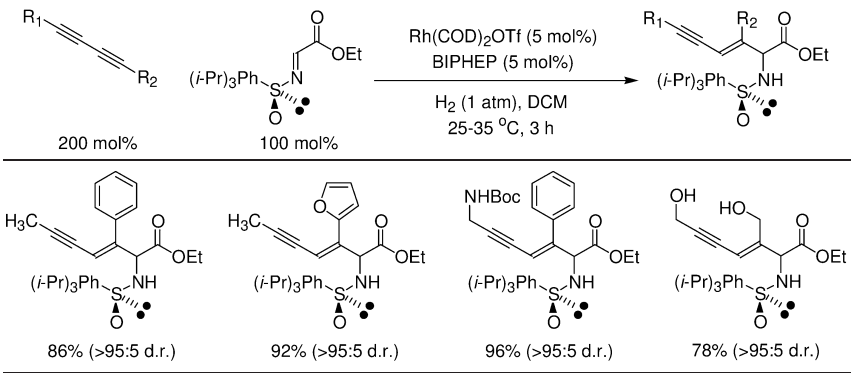
Scheme 22.16 Competition experiments reveal reductive coupling occurs chemoselectively with the strongest π-acid.

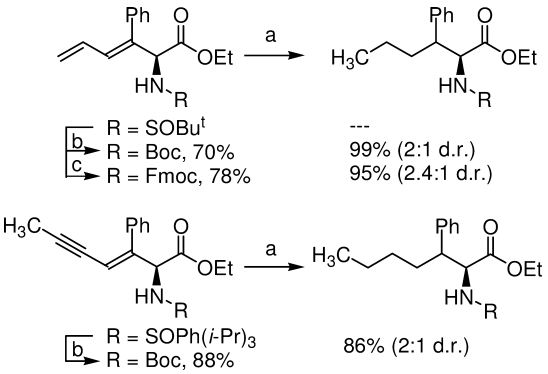
Table 22.9 Reductive coupling of 1,3-enynes with ethyl (*N-tert*-butanesulfinyl)iminoacetate.



a) $Rh(PPh_3)_3Cl$ (10 mol%), H_2 (1 atm), toluene, 25 °C, 18 h.

Table 22.10 Reductive coupling of 1,3-diynes with ethyl (*N*-2,4,6-triisopropylbenzenesulfinyl)iminoacetate.





Scheme 22.17 Exhaustive hydrogenation of diene- and enyne-containing reductive coupling products using Crabtree's catalyst.

using Crabtree's catalyst also proceeds readily. However, the *N-tert*-butanesulfinyl residue must be exchanged for a carbamate protecting group (Scheme 22.17).

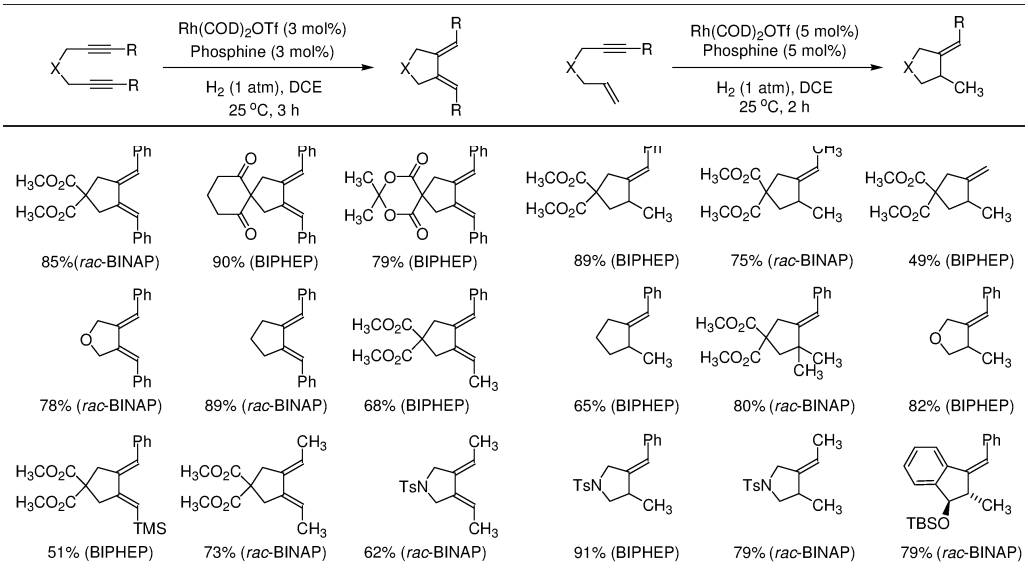
22.5
Reductive Cyclization of 1,6-Diynes and 1,6-Enynes

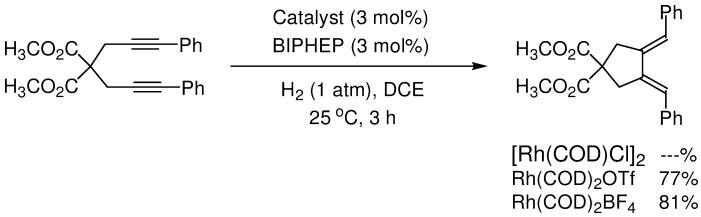
Hydrogenation of 1,6-diynes using cationic rhodium precatalysts promotes reductive cyclization to afford 1,2-dialkylidenecycloalkane products. As for all hydrogen-mediated C–C bond formations described in this account, cationic rhodium precatalysts are required. Whereas reductive cyclization proceeds readily using $Rh(COD)_2OTf$ and $Rh(COD)_2BF_4$, the neutral precatalyst $[Rh(COD)Cl]_2$ is ineffective (Scheme 22.18) [27, 38]. Under optimized conditions, reductive cyclization proceeds smoothly across a range of 1,6-diynes. Near-identical hydrogenation conditions are effective for the reductive cyclization of 1,6-enynes [39, 40]. Notably, conformationally predisposed substrates possessing geminal substitution in the tether are not necessary (Table 22.11).

Enantioselective hydrogenation of 1,6-enynes using chirally modified cationic rhodium precatalysts enables enantioselective reductive cyclization to afford alkylidene-substituted carbocycles and heterocycles [27b, 41, 42]. Good to excellent yields and exceptional levels of asymmetric induction are observed across a structurally diverse set of substrates. For systems that embody 1,2-disubstituted alkenes, competitive β-hydride elimination *en route* to products of cycloisomerization is observed. However, related enone-containing substrates cannot engage in β-hydride elimination, and undergo reductive cyclization in good yield (Table 22.12).

The products of reductive cyclization incorporate two non-exchangeable hydrogen atoms. Homolytic and heterolytic hydrogen activation pathways may now be discriminated on the basis of hydrogen-deuterium crossover experiments. Reductive cyclization of the indicated nitrogen-tethered enyne under a mixed atmosphere

Table 22.11 Reductive cyclization of assorted 1,6-diynes and 1,6-enynes.



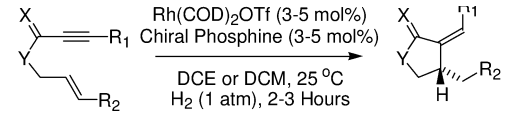


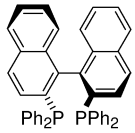
Scheme 22.18 Reductive cyclization of 1,6-diynes.

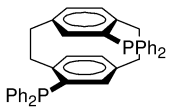
of H_2 and D_2 or under an atmosphere of DH does not provide crossover products, in accordance with homolytic hydrogen activation. Interestingly, exposure of related systems incorporating a *cis*-1,2-disubstituted alkene to identical conditions under a D_2 atmosphere does not induce reductive cyclization. Rather, products of cycloisomerization are formed. A hydrometallative mechanism for cycloisomerization would be initiated by D_2 oxidative addition and propagated by rhodium hydrides derived upon β-hydride elimination from intermediate **A**. Deuterium incorporation should occur in the first turnover of the catalytic cycle, yet deuterium incorporation is not observed, even at stoichiometric catalyst loadings. The extent of deuterium incorporation for the isotopically labeled reaction products is determined by electrospray ionization-mass spectrometry (ESI-MS) analysis with isotopic correction and is corroborated by ^{1}H-NMR analysis (Scheme 22.19).

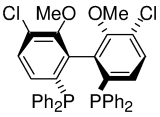
The acquisition of cycloisomerization products without deuterium incorporation is inconsistent with a hydrometallative mechanism. Furthermore, the ab-

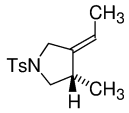
Table 22.12 Enantioselective reductive cyclization of 1,6-enynes.

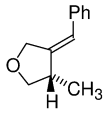


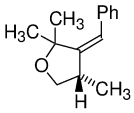

(*R*)-BINAP

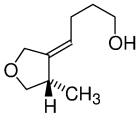

(*R*)-PHANEPHOS

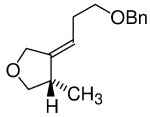

(*R*)-Cl,OMe-BIPHEP

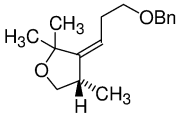

A: 69%, 94% e.e.
B: 79%, 93% e.e.
C: multiple products

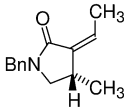

A: 84%, 95% e.e.
B: 80%, 97% e.e.
C: multiple products

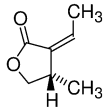

A: 85%, 84% e.e.
B: 76%, 82% e.e.
C: multiple products

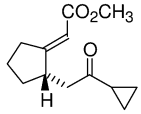

A: 77%, 95% e.e.
B: 75%, 95% e.e.
C: multiple products

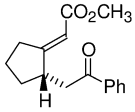

A: 75%, 98% e.e.
B: 77%, 98% e.e.
C: multiple products

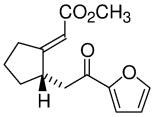

A: 82%, 98% e.e.
B: 64%, 98% e.e.
C: multiple products

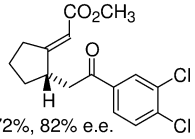

A: 40%, 26% e.e.
B: 24%, 10% e.e.
C: 73%, 91% e.e.

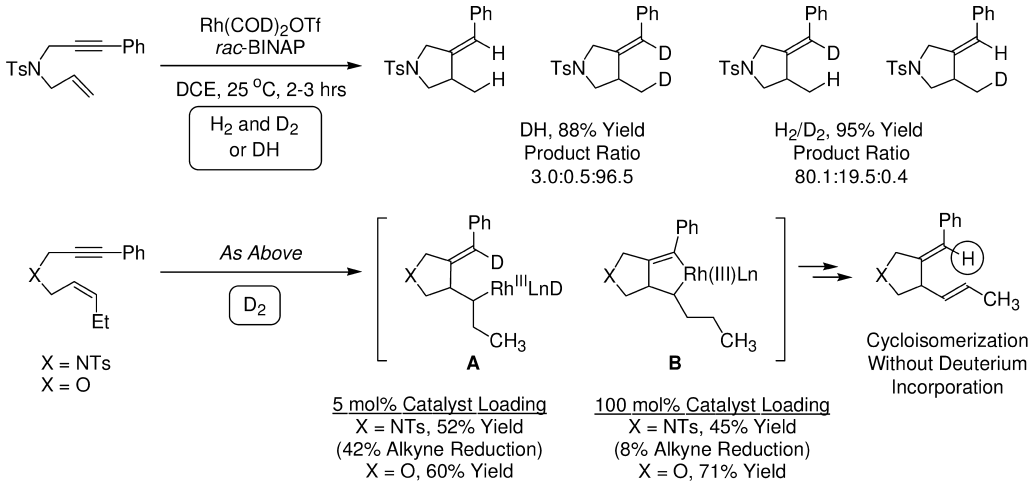

A: 89%, 6% e.e.
B: 79%, 20% e.e.
C: 73%, 94% e.e.


A: 68%, 98% e.e.
B: 63%, 90% e.e.
C: complete reduction


A: 78%, 88% e.e.
B: 66%, 96% e.e.
C: complete reduction


A: 65%, 95% e.e.
B: 72%, 96% e.e.
C: complete reduction


A: 72%, 82% e.e.
B: 63%, 94% e.e.
C: complete reduction



Scheme 22.19 Mechanistic studies involving hydrogen-deuterium crossover experiments, along with the observance of non-conjugated cycloisomerization products, suggest that rhodium(III) metallocyclopentene formation occurs in advance of hydrogen activation.

sence of conjugated cycloisomerization products suggests β-hydride elimination from metallocycle **B**. If indeed oxidative cyclization occurs initially to form metallocycle **B** [17], subsequent hydrogenolytic cleavage must occur via: (i) hydrogen oxidative addition or (ii) hydrogen activation via σ-bond metathesis [37c]. Whereas hydrogen oxidative addition to a Rh(III) metallocycle would afford a Rh(V) intermediate, hydrogen activation via σ-bond metathesis would not. In either case, it would appear that C–C bond formation occurs in advance of hydrogen activation. Hydrogen oxidative addition followed by rhodium(V) metallocycle formation is unlikely and, to our knowledge, without precedent. Finally, it is worth noting that hydrogen oxidative addition is rate-determining for asymmetric hydrogenations catalyzed by cationic rhodium complexes, which suggests that the oxidative cyclization manifold may compete favorably with hydrogen oxidative addition [28].

22.6 Conclusion

From the seminal studies of Sabatier [43] and Adams [44] to the more recent studies of Knowles [45] and Noyori [46], catalytic hydrogenation has been regarded as a method of reduction. The results herein demonstrate the feasibility of transforming catalytic hydrogenation into a powerful and atom-economical method for reductive C–C bond formation. Given the profound socioeconomic impact of alkene hydroformylation, the development of catalysts for the hydrogen-mediated

coupling of basic feedstocks, such as α-olefins and styrenes with aldehyde partners, represents a paramount scientific challenge. The mechanistic underpinnings of these transformations have begun to unfold. Hydrogen-mediated enone couplings require mild basic additives and, hence, likely involve heterolytic hydrogen activation by way of an intermediate dihydride. In contrast, the mechanistic data linked to the reductive coupling of conjugated dienes, enynes, and diynes to α-ketoaldehydes and related iminoacetates, along with data pertaining to the reductive cyclizations of 1,6-diynes and 1,6-enynes, suggest oxidative coupling to form metallacyclic intermediates which are then hydrogenolytically cleaved. This oxidative coupling-hydrogenolysis motif should play a key role in the design of related hydrogen-mediated couplings. It is the authors hope that the emergent mechanistic principles gleaned from these initial studies will ultimately spawn a broad new class of hydrogen-mediated C–C couplings.

Acknowledgments

The authors acknowledge the Robert A. Welch Foundation (F-1466), the Research Corporation Cottrell Scholar Award, the National Science Foundation CAREER Award, the Alfred P. Sloan Foundation, the Camille and Henry Dreyfus Foundation, Eli Lilly, and Merck.

Abbreviations

MVK methyl vinyl ketone
PVK phenyl vinyl ketone

References

1 For use of alkenes as nucleophilic partners in catalytic reductive couplings, see: (a) N. M. Kablaoui, S. L. Buchwald, *J. Am. Chem. Soc.* **1995**, *117*, 6785; (b) W. E. Crowe, M. J. Rachita, *J. Am. Chem. Soc.* **1995**, *117*, 6787; (c) N. M. Kablaoui, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 3182.

2 For use of alkynes as nucleophilic partners in catalytic hydrometallative reductive couplings to aldehydes, see: (a) E. Oblinger, J. Montgomery, *J. Am. Chem. Soc.* **1997**, *119*, 9065; (b) X.Q. Tang, J. Montgomery, *J. Am. Chem. Soc.* **1999**, *121*, 6098; (c) W.-S. Huang, J. Chen, T. F. Jamison, *Org. Lett.* **2000**, *2*, 4221; (d) E. A. Colby, T. F. Jamison, *J. Org. Chem.* **2003**, *68*, 156; (e) K. M. Miller, W.-S. Huang, T. F. Jamison, *J. Am. Chem. Soc.* **2003**, *125*, 3442; (f) K. Takai, S. Sakamoto, T. Isshiki, *Org. Lett.* **2003**, *5*, 653; (g) J. Chan, T. F. Jamison, *J. Am. Chem. Soc.* **2003**, *125*, 11514; (h) E. A. Colby, K. C. O'Brien, T. F. Jamison, *J. Am. Chem. Soc.* **2004**, *126*, 998; (i) J. Chan, T. F. Jamison, *J. Am. Chem. Soc.* **2004**, *126*, 10682; (j) K. M. Miller, T. F. Jamison, *J. Am. Chem. Soc.* **2004**, *126*, 15342.

3 For use of alkynes as nucleophilic partners in catalytic hydrometallative reductive couplings to imines, see: S.J. Patel,

T.F. Jamison, *Angew. Chem. Int. Ed.* **2003**, *42*, 1364.

4 For use of alkynes as nucleophilic partners in catalytic hydrometallative reductive couplings to imines, see: (a) M.V. Chevliakov, J. Montgomery, *J. Am. Chem. Soc.* **1999**, *121*, 11139; (b) J. Montgomery, M. Song, *Org. Lett.* **2002**, *4*, 4009; (c) K.K.D. Amarasinghe, J. Montgomery, *J. Am. Chem. Soc.* **2002**, *124*, 9366.

5 For use of conjugated enones as nucleophilic partners in catalytic intermolecular reductive couplings to aldehydes, see: (a) A. Revis, T.K. Hilty, *Tetrahedron Lett.* **1987**, *28*, 4809; (b) S. Isayama, T. Mukaiyama, *Chem. Lett.* **1989**, 2005; (c) I. Matsuda, K. Takahashi, S. Sato, *Tetrahedron Lett.* **1990**, *31*, 5331; (d) S. Kiyooka, A. Shimizu, S. Torii, *Tetrahedron Lett.* **1998**, *39*, 5237; (e) T. Ooi, K. Doda, D. Sakai, K. Maruoka, *Tetrahedron Lett.* **1999**, *40*, 2133; (f) S.J. Taylor, J.P. Morken, *J. Am. Chem. Soc.* **1999**, *121*, 12202; (g) S.J. Taylor, M.O. Duffey, J.P. Morken, *J. Am. Chem. Soc.* **2000**, *122*, 4528; (h) C.-X. Zhao, M.O. Duffey, S.J. Taylor, J.P. Morken, *Org. Lett.* **2001**, *3*, 1829; (i) C.-X. Zhao, J. Bass, J.P. Morken, *Org. Lett.* **2001**, *3*, 2839.

6 For use of conjugated enones as nucleophilic partners in catalytic intramolecular reductive couplings to aldehydes, see: (a) T.-G. Baik, A.L. Luis, L.-C. Wang, M.J. Krische, *J. Am. Chem. Soc.* **2001**, *123*, 5112; (b) D. Emiabata-Smith, A. McKillop, C. Mills, W.B. Motherwell, A.J. Whitehead, *Synlett* **2001**, 1302; (c) L.-C. Wang, H.-Y. Jang, Y. Roh, V. Lynch, A.J. Schultz, X. Wang, M.J. Krische, *J. Am. Chem. Soc.* **2002**, *124*, 9448; (d) R.R. Huddleston, D.F. Cauble, M.J. Krische, *J. Org. Chem.* **2003**, *68*, 11; (e) M. Freiria, A.J. Whitehead, D.A. Tocher, W.B. Motherwell, *Tetrahedron* **2004**, *60*, 2673.

7 For use of conjugated enones as nucleophilic partners in catalytic intermolecular reductive couplings to aldimines, see: (a) J.A. Townes, M.A. Evans, J. Queffelec, S.J. Taylor, J.P. Morken, *Org. Lett.* **2002**, *4*, 2537; (b) T. Muraoka, S.-I. Kamiya, I. Matsuda, K. Itoh, *Chem. Commun.* **2002**, 1284.

8 For use of conjugated dienes as nucleophilic partners in catalytic intramolecular reductive couplings to aldehydes, see: (a) Y. Sato, M. Takimoto, K. Hayashi, T. Katsuhara, K. Tagaki, M. Mori, *J. Am. Chem. Soc.* **1994**, *116*, 9771; (b) Y. Sato, Y. Takimoto, M. Mori, *Tetrahedron Lett.* **1996**, *37*, 887; (c) Y. Sato, T. Takanashi, M. Hoshiba, M. Mori, *Tetrahedron Lett.* **1998**, *39*, 5579; (d) Y. Sato, N. Saito, M. Mori, *J. Am. Chem. Soc.* **2000**, *122*, 2371; (e) K. Shibata, M. Kimura, M. Shimizu, Y. Tamaru, *Org. Lett.* **2001**, *3*, 2181; (f) Y. Sato, N. Saito, M. Mori, *J. Org. Chem.* **2002**, *67*, 9310; (g) Y. Sato, T. Takanishi, M. Hoshiba, M. Mori, *J. Organomet. Chem.* **2003**, *688*, 36.

9 For use of conjugated dienes as nucleophilic partners in catalytic intermolecular reductive couplings to aldehydes, see: (a) M. Kimura, A. Ezoe, K. Shibata, Y. Tamaru, *J. Am. Chem. Soc.* **1998**, *120*, 4033; (b) M. Kimura, H. Fujimatsu, A. Ezoe, K. Shibata, M. Shimizu, S. Matsumoto, Y. Tamaru, *Angew. Chem. Int. Ed.* **1999**, *38*, 397; (c) M. Kimura, K. Shibata, Y. Koudahashi, Y. Tamaru, *Tetrahedron Lett.* **2000**, *41*, 6789; (d) M. Kimura, A. Ezoe, S. Tanaka, Y. Tamaru, *Angew. Chem. Int. Ed.* **2001**, *40*, 3600; (e) T.-P. Loh, H.-Y. Song, Y. Zhou, *Org. Lett.* **2002**, *4*, 2715; (f) Y. Sato, R. Sawaki, N. Saito, M. Mori, *J. Org. Chem.* **2002**, *67*, 656; (g) L. Bareille, P. Le Gendre, C. Moise, *Chem. Commun.* **2005**, 775.

10 For use of conjugated dienes as nucleophilic partners in catalytic intermolecular reductive couplings to aldimines, see: M. Kimura, A. Miyachi, K. Kojima, S. Tanaka, Y. Tamaru, *J. Am. Chem. Soc.* **2004**, *126*, 14360.

11 For use of conjugated enynes as nucleophilic partners in catalytic intermolecular reductive couplings to aldehydes, see: K.M. Miller, T. Luanphaisarnnont, C. Molinaro, T.F. Jamison, *J. Am. Chem. Soc.* **2004**, *126*, 4130.

12 For reviews on atom economy, see: (a) B.M. Trost, *Science* **1991**, *254*, 1471; (b) B.M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259.

13 (a) P.J. Black, M.G. Edwards, J.M.J. Williams, *Tetrahedron* **2005**, *61*, 1363;

(b) M.G. Edwards, R.F.R. Jazzar, B.M. Paine, D.J. Shermer, M.K. Whittlesey, J.M.J. Williams, D.D. Edney, *Chem. Commun.* **2004**, 90; (c) G. Cami-Kobeci, J.M.J. Williams, *Chem. Commun.* **2004**, 1072; (d) M.G. Edwards, J.M.J. Williams, *Angew. Chem. Int. Ed.* **2002**, *41*, 4740; (e) P.J. Black, W. Harris, J.M.J. Williams, *Angew. Chem. Int. Ed.* **2001**, *40*, 4475.

14 For recent reviews on alkene hydroformylation and the Fischer-Tropsch reaction, see: (a) B. Breit, *Acc. Chem. Res.* **2003**, *36*, 264; (b) B. Breit, W. Seiche, *Synthesis* **2001**, 1; (c) W.A. Herrmann, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 117; (d) C.-K. Rofer-Depoorter, *Chem. Rev.* **1981**, *81*, 447.

15 Prior to our work, two examples of hydrogen-mediated C–C bond formation under CO-free conditions are reported: (a) G.A. Molander, J.O. Hoberg *J. Am. Chem. Soc.* **1992**, *114*, 3123; (b) K. Kokubo, M. Miura, M. Nomura, *Organometallics* **1995**, *14*, 4521.

16 For reviews on the heterolytic activation of elemental hydrogen, see: (a) P.J. Brothers, *Prog. Inorg. Chem.* **1981**, *28*, 1; (b) G. Jeske, H. Lauke, H. Mauermann, H. Schumann, T.J. Marks, *J. Am. Chem. Soc.* **1985**, *107*, 8111.

17 Rh(III)-metallocycles derived from 1,6-enynes are postulated as reactive intermediates in catalytic [4+2] and [5+2] cycloadditions, Pauson-Khand reactions and cycloisomerizations: P. Cao, B. Wang, X. Zhang, *J. Am. Chem. Soc.* **2000**, *122*, 64901 and references cited therein.

18 (a) C.A. Tolman, P.Z. Meakin, D.L. Lindner, J.P. Jesson, *J. Am. Chem. Soc.* **1974**, *96*, 2762; (b) J. Halpern, T. Okamoto, A. Zakhariev, *J. Mol. Catal.* **1976**, *2*, 65.

19 For a review, see: L. Marko, *Pure Appl. Chem.* **1979**, *51*, 2211.

20 Monohydride formation by deprotonation of a dihydride intermediate is known for cationic Rh-complexes: (a) R.R. Schrock, J.A. Osborn, *J. Am. Chem. Soc.* **1976**, *98*, 2134; (b) R.R. Schrock, J.A. Osborn, *J. Am. Chem. Soc.* **1976**, *98*, 2143; (c) R.R. Schrock, J.A. Osborn, *J. Am. Chem. Soc.* **1976**, *98*, 4450.

21 For a review of the acidity of metal hydrides, see: J.R. Norton, in: A. Dedieu (Ed.), *Transition Metal Hydrides*. New York, **1992**, pp. 309.

22 Direct heterolytic activation of hydrogen by $RhCl(CO)(PPh_3)_2$ has been suggested, but likely involves an intermediate dihydride: D. Evans, J.A. Osborn, G. Wilkinson, *J. Chem. Soc. A* **1968**, 3133.

23 For earlier reviews encompassing aspects of this work, see: (a) H.-Y. Jang, M.J. Krische, *Eur. J. Org. Chem.* **2004**, 3953; (b) H.-Y. Jang, M.J. Krische, *Acc. Chem. Res.* **2004**, *37*, 653; (c) H.-Y. Jang, R.R. Huddleston, M.J. Krische, *Chemtracts* **2003**, *16*, 554.

24 (a) H.-Y. Jang, R.R. Huddleston, M.J. Krische, *J. Am. Chem. Soc.* **2002**, *124*, 15156; (b) R.R. Huddleston, M.J. Krische, *Org. Lett.* **2003**, *5*, 1143; (c) G.A. Marriner, S.A. Garner, H.-Y. Jang, M.J. Krische, *J. Org. Chem.* **2004**, *69*, 1380; (d) P.K. Koech, M.J. Krische, *Org. Lett.* **2004**, *6*, 691; (e) S.A. Garner, C.-K. Jung, M.J. Krische, *Org. Lett.* **2006**, *8*, 519.

25 H.-Y. Jang, R.R. Huddleston, M.J. Krische, *Angew. Chem. Int. Ed.* **2003**, *42*, 4074.

26 (a) H.-Y. Jang, R.R. Huddleston, M.J. Krische, *J. Am. Chem. Soc.* **2004**, *126*, 4664; (b) R.R. Huddleston, H.-Y. Jang, M.J. Krische, *J. Am. Chem. Soc.* **2003**, *125*, 11488; (c) J.-R. Kong, C.-W. Cho, M.J. Krische, *J. Am. Chem. Soc.* **2005**, *127*, 11269.

27 (a) H.-Y. Jang, M.J. Krische, *J. Am. Chem. Soc.* **2004**, *126*, 7875; (b) H.-Y. Jang, F.W. Hughes, H. Gong, J. Zhang, J.S. Brodbelt, M.J. Krische, *J. Am. Chem. Soc.* **2004**, *127, 6174.*

28 For excellent reviews, see: (a) J. Halpern, *Asymm. Synth.* **1985**, *5*, 41; (b) C.R. Landis, T.W. Brauch, *Inorg. Chim. Acta* **1998**, *270*, 285; (c) I. Gridnev, T. Imamoto, *Acc. Chem. Res.* **2004**, *37*, 633.

29 A method for the stoichiometric addition of metallo-aldehyde enolates to ketones has recently been reported: K. Yachi, H. Shinokubo, K. Oshima, *J. Am. Chem. Soc.* **1999**, *121*, 9465.

30 E.M. Arnett, F.J. Fisher, M.A. Nichols, A.A. Ribeiro, *J. Am. Chem. Soc.* **1989**, *111*, 748.

31 The failure of *tris*(dialkylamino)sulfonium enolates to react with aldehydes is

attributed to unfavorable enolate-aldolate equilibria: (a) R. Noyori, J. Sakata, M. Nishizawa, *J. Am. Chem. Soc.* **1980**, *102*, 1223; (b) R. Noyori, I. Nishida, J. Sakata, *J. Am. Chem. Soc.* **1981**, *103*, 2106; (c) R. Noyori, I. Nishida, J. Sakata, *J. Am. Chem. Soc.* **1983**, *105*, 1598.

32 (a) C. H. Heathcock, in: B. M. Trost, I. Fleming, C. H. Heathcock (Eds.), *Comprehensive Organic Synthesis: Additions to C-X Bonds Part 2*. Pergamon Press, New York, pp. 181; (b) B. Alcaide, P. Almendros, *Angew. Chem. Int. Ed.* **2003**, *42*, 858.

33 (a) S. Denmark, S. K. Ghosh, *Angew. Chem. Int. Ed.* **2001**, *40*, 4759; (b) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798; (c) C. Pidathala, L. Hoang, N. Vignola, B. List, *Angew. Chem. Int. Ed.* **2003**, *42*, 2785.

34 For a recent discussion, see: T. C. Morrill, C. A. D'Souza, *Organometallics* **2003**, *22*, 1626 and references therein.

35 (a) M. J. S. Dewar, *Bull. Soc. Chim. Fr.* **1951**, *18*, C71; (b) J. Chatt, L. A. Duncanson, *J. Chem. Soc.* **1953**, 2939.

36 For a review, see: F. Sato, H. Urable, S. Okamoto, *Chem. Rev.* **2000**, *100*, 2835.

37 For σ-bond metathesis involving Rh(III) intermediates, see: (a) J. F. Hartwig, K. S. Cook, M. Hapke, C. D. Incarvito, Y. Fan, C. E. Webster, M. B. Hall, *J. Am. Chem. Soc.* **2005**, *127*, 2538; (b) C. Liu, R. A. Widenhoefer, *Organometallics* **2002**, *21*, 5666; (c) F. Hutschka, A. Dedieu, W. Leitner, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1742.

38 For metal-catalyzed cyclization of 1,6- and 1,7-diynes, see: (a) B. M. Trost, D.C. Lee, *J. Am. Chem. Soc.* **1988**, *110*, 7255; (b) K. Tamao, K. Kobayashi, Y. Ito, *J. Am. Chem. Soc.* **1989**, *111*, 6478; (c) B. M. Trost, F. J. Fleitz, W. J. Watkins, *J. Am. Chem. Soc.* **1996**, *110*, 5146; (d) M. Lautens, N. D. Smith, D. Ostrovsky, *J. Org. Chem.* **1997**, *62*, 8970; (e) S.-Y. Onozawa, Y. Hatanaka, M. Tanaka, *Chem. Commun.* **1997**, 1229; (f) S.-Y. Onozawa, Y. Hatanaka, N. Choi, M. Tanaka, *Organometallics* **1997**, *16*, 5389; (g) I. Ojima, J. Zhu, E. S. Vidal, D. F. Kass, *J. Am. Chem. Soc.* **1998**, *120*, 6690; (h) T. Muraoka, I. Matsuda, K. Itoh, *Tetrahedron Lett.* **1998**, *39*, 7325; (i) S. Gréau, B. Radetich, T. V. RajanBabu, *J. Am. Chem. Soc.* **2000**, *122*, 8579; (j) J. W. Madine, X. Wang, R. A. Widenhoefer, *Org. Lett.* **2001**, *3*, 385; (k) X. Wang, H. Chakrapani, J. W. Madine, M. A. Keyerleber, R.A. Widenhoefer, *J. Org. Chem.* **2002**, *67*, 2778; (l) T. Muraoka, I. Matsuda, K. Itoh, *Organometallics* **2002**, *21*, 3650; (m) C. Liu, R. A. Widenhoefer, *Organometallics* **2002**, *21*, 5666; (n) T. Uno, S. Wakayanagi, Y. Sonoda, K. Yamamoto, *Synlett* **2003**, 1997; (o) B. M. Trost, M. T. Rudd, *J. Am. Chem. Soc.* **2003**, *125*, 11516.

39 For reviews encompassing the Pd-catalyzed cycloisomerization and reductive cyclization of 1,6-enynes, see: (a) B. M. Trost, *Acc. Chem. Res.* **1990**, *23*, 34; (b) I. Ojima, M. Tzamarioudaki, Z. Li, R. J. Donovan, *Chem. Rev.* **1996**, *96*, 635; (c) B. M. Trost, M. J. Krische, *Synlett* **1998**, 1; (d) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813.

40 For selected examples of the cycloisomerization of 1,6-enynes catalyzed by metals other than palladium, see: (a) Titanium: S. J. Sturla, N. M. Kablaoui, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 1976; (b) Rhodium: P. Cao, B. Wang, X. Zhang, *J. Am. Chem. Soc.* **2000**, *122*, 6490; (c) Nickel-Chromium: B. M. Trost, J. M. Tour, *J. Am. Chem. Soc.* **1987**, *109*, 5268; (d) Ruthenium: M. Nishida, N. Adachi, K. Onozuka, H. Matsumura, M. Mori, *J. Org. Chem.* **1998**, *63*, 9158; (e) B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **2000**, *122*, 714; (f) J. LaPaih, D. C. Rodriguez, S. Derien, P. H. Dixneuf, *Synlett* **2000**, 95; (g) Cobalt: A. Ajamian, J. L. Gleason, *Org. Lett.* **2003**, *5*, 2409; (h) Iridium: N. Chatani, H. Inoue, T. Morimoto, T. Muto, S. Muria, *J. Org. Chem.* **2001**, *66*, 4433.

41 For an excellent review covering enantioselective metal-catalyzed cycloisomerization of 1,6- and 1,7-enynes, see: I. J. S. Fairlamb, *Angew. Chem. Int. Ed.* **2004**, *43*, 1048.

42 For rhodium-catalyzed enantioselective enyne cycloisomerization and hydrosilylation-cyclization, see: (a) C. Ping, X. Zhang, *Angew. Chem. Int. Ed.* **2000**, *39*, 4104; (b) A. Lei, M. He, S. Wu, X.

Zhang, *Angew. Chem. Int. Ed.* **2002**, *41*, 3457–3460; (c) A. Lei, J. P. Waldkirch, M. He, X. Zhang, *Angew. Chem. Int. Ed.* **2002**, *41*, 4526; (d) A. Lei, M. He, X. Zhang, *J. Am. Chem. Soc.* **2003**, *125*, 11472; (e) H. Chakrapani, C. Liu, R. A. Widenhoefer, *Org. Lett.* **2003**, *5*, 157.

43 For a biographical sketch of Paul Sabatier, see: A. Lattes, *C. R. Acad. Sci. Ser. IIC: Chemie* **2000**, *3*, 705.

44 For a biographical sketch of Roger Adams, see: D.S. Tarbell, A.T. Tarbell, *J. Chem. Ed.* **1979**, *56*, 163.

45 (a) W. S. Knowles, *Prix Nobel* **2001**, *2002*, 160; (b) W. S. Knowles, *Angew. Chem. Int. Ed.* **2002**, *41*, 1998; (c) W. S. Knowles, *Adv. Synth. Catal.* **2003**, *345*, 3.

46 (a) R. Noyori, *Prix Nobel* **2001**, *2002*, 186; (b) R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008; (c) R. Noyori, *Adv. Synth. Catal.* **2003**, *345*, 15.